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LABORATORY RESULTS THAT SUGGEST USING PROGNOSTIC MARKERS IN THE ASSESSMENT AND DIAGNOSIS OF RHEUMATOID ARTHRITIS

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Abstract

ESR and CRP reactants reflect synovitis indirectly. Simultaneously, they are the cause of objectivization and measurement of immune-mediated inflammatory responses in RA. CRP, RF, and ESR testing accompanied with clinical variables of inflammatory synovitis are suggested to evaluate the disease's activity.

Aim: Assessment of RA's activity with the reactants of the acute phase, ESR, CRP, and RF as prognostic markers for disease activity in patients treated with Methotrexate for early RA.

This study focuses on 70 patients in total: 35 patients with early RA and 35 patients in the healthy control group. Patients (pts) were given Methotrexate once a week at a dose of 10 mg on average. We were able to analyze ESR, RF, and CRP in every patient at certain time intervals (0 times, after 6, 9, and 12 months).

RA was assessed following the dynamics of changes in the mean values of CRP, RF, and ESR. The analysis showed statistically notable differences among the mean values of ESR in the four-time intervals (p=0,00002). The mean values of CRP also showed differences in all four-time intervals (p=0,0428). On the other hand, no noteworthy statistical differences were detected among the mean values of RF in the four-time intervals (p=0,573). High values of CRP and RF were detected in most patients.

The process of disease progression continues despite the Methotrexate therapy, especially in those patients that have elevated values of ESR, CRP, and RF. They are shown to be predictors of the aggressive course of the disease. This enables the selection of the high-risk group of patients for an aggressive course of the disease and points to the necessity for early and aggressive treatment.

***Keywords*:** RA (Rheumatoid Arthritis); RF (Rheumatoid Factor); reactants of the acute phase; CRP.

Introduction

Rheumatoid arthritis or RA is an inflammatory, autoimmune, and chronic disease that causes inflammation in affected parts of the body (mainly joints). RA can affect every joint, however, it mostly affects the small hand joints. The reason for the permanent destructive changes of the joint cartilage and the subchondral bone is chronic synovitis most of the time. ESR and CRP's reactants secondarily reflect synovitis. [1-8].

Simultaneously, they are the cause of objectivization and measurement of immune-mediated inflammatory responses in RA. CRP, RF, and ESR testing accompanied with clinical variables of inflammatory synovitis are suggested to evaluate the activity of the disease. Serial measurements of ESR and CRP are recommended for credible evaluation of RA.

Some studies report that despite the correlation between radiographic progression and the reactants of the acute phase, the progression of erosion continues although there is suppression of the joint inflammation.

According to laboratory tests, thrombocytopenia and anaemia are also causes of inflammation in RA. The Rheumatoid factor (IgM-RF) represents an anti-immunoglobulin antibody that acts directly on the Fc fragment of the immunoglobulin G. A high titer of RF has been associated with the progressive course of the disease, so consequently, RF has been detected in 78-80% of the patients. The best predictors for a bad prognosis, especially in patients with early RA, are SAARD (antirheumatic drugs that slow down the disease). [9]. From a clinical point of view, however, prediction of the outcome of the disease in patients with early RA is not possible.

Aim

This study aims to assess the activity of RA with the reactants of the acute phase, ESR, CRP, and RF as prognostic markers for disease activity in patients with RA that have been given the drug Methotrexate.

Material and methods

Patients included in this study should satisfy at least 4 of the 7 proposed points of criteria by the American Association for Rheumatism (ARA) from 1987. The criteria from 1 to 4 should be present for at least 6 weeks. This study consists of 35 patients suffering from RA of whom 28 women and 7 men and 35 patients of whom 18 women and 17 men were in the healthy control group. The mean age in the RA group was 56,68 (+/- 6,79) (40-65), and the healthy control group's mean age was 46,2 (+/- 12,79) (9-65).

The mean duration of the disease was 43,97 (+/- 45,23) months in 6-168 months.

There were examinations in several time points, 0 time, 6, 9, and 12 months. Methotrexate was first indicated once a week with an average dose of 10 mg, accompanied by non-steroidal antirheumatic therapy. None of the patients has a history of the disease.

Clinical evaluation of the disease activity

This evaluation was conducted by subspecialists in the field. Disease activity was evaluated using the DAS 28 index (Disease Activity Score- DAS 28).

This index uses a mathematical formula to acquire a unique composite quantitative score that consists of palpatory pain joints (maximal number 28), swollen joints (maximal number 28), ESR Westergren, global patient assessment for disease activity (0-100 mm Visual Analogue Scale - VAS), and morning stiffness (minutes). The DAS 28 index ranged between 0-10 and the score <3.2 indicates low active disease. [10-14].

Including criteria

There were patients ranging from 18 to 65 years old in the study with recently diagnosed RA and untreated.

Excluding criteria

All patients with any diseases and/or conditions that could affect the results directly or indirectly, including:

1. Pts with a history of the spleen, thyroid gland, liver, kidney, haematological, cardiovascular, lung, neurological, and auto-immune diseases and disorders, all aged <18 years old;
2. Pts suffering from diabetes, acute infections, febrile conditions, and malignant diseases;
3. Pts with uric arthritis, SLE, mixed connective tissue diseases, vasculitis, and urine infections;
4. Pts that have a history of blood transfusions and overweight patients;
5. Pts are treated with drugs from the basic line;

6. Pts that in the 0 times showed signs of hyperglycemia and/or elevated degradation products such as serum and urine creatinine, arterial hypertension, serum urea and enzymes disorder.

All participants engaged in the study voluntarily. The ethical criteria for the study have been met.

Laboratory evaluation

To obtain a precise clinical evaluation of the disease, it was necessary to calculate some laboratory variables: differential blood count, complete blood count (CBC), ACPA antibodies, reactants of the acute phase, Rheumatoid factor (RF), C-reactive protein (CRP), alanine aminotransferase (ALT), alkaline phosphatase (AP), aspartate aminotransferase (AST), creatine kinase (CK), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), serum urea, and creatinine.

The quantitative method to determine ESR is the Westergren method. The normal values are 7-8 MM for men and 11-16 MM for women. The agglutination test or the Latex CRP test is used to determine CRP. The values are <6 mg/L CRP in the serum. The same agglutination test or the Latex CRP test is used to determine RF. The referent values are <30 IU/ml RF in the serum. The manufacturer DIA-STAT™ Anti-CCP from Axis-Shield Diagnostics determines the ACPA antibodies. It is a semi-quantitative/qualitative ELISA test that detects IgG autoantibodies in the human plasma or serum. The results for the quantitative protocol are estimated through the absorbent value (optic density) from positive and negative control and for every sample.

Statistical Analysis

We used Freedman's analysis of variance to determine the differences among the arithmetic means in the groups. This testing was made with the Wilcoxon Matched Pairs test where the P-value between 0,05 and 0,1 was considered statistically significant.

Results

Table 1. Mean values of RF, ESR and CRP in time intervals in RA.

Time intervals in RA up to 1 year	Mean values of RF JU/ml RF<30JU/ml (neg)	Mean values of ESR (mm/h)	Mean values of CRP mg/l CRP<6 mg/l (neg)
0 time	195,5 ± 289,9	59,9 ± 27,7	26,3 ± 28,8
After 6 months	494,4 ± 366,1	31,6 ± 16,9	19,0 ± 24,0
After 9 months	89,3 ± 157,9	31,4 ± 17,4	10,6 ± 11,9
After 12 months	123 ± 311,7	25,0 ± 11,6	13,4 ± 22,1

1. There were statistically significant differences in mean values of ESR in time intervals between 0 time and 6 months (p=0,00014), between 0 time and 9 months (p=0,00014), and between 0 time and 12 months (p=0,00010). Fridman's analysis of variance also showed significant differences between the mean values of ESR in the four-time intervals - Fr 2 =19.485 p=0.00002. There was a consecutive decline of ESR in the values in every other control in certain time intervals amongst most of the patients.
2. The mean values of CRP showed statistically significant differences (using Fridman's analysis of variance) in the four-time intervals - Fr $x2$ = 2.804 p = 0.0428 (standard deviations showed great

variations). The number of patients whose CRP values were negative increased after some time. The differences were statistically significant (x 2 = 11.35 df = 3 p = 0.0099).

3. The mean values of RF did not show any significant differences in the four-time intervals using Fridman's analysis. -Frx^2 = 1.017 p = 0.3875 (standard deviations showed great differences). The number of patients whose values for RF were negative grew over time, however, the differences were not significant statistically. ($x2 = 1.99;$; df =3; p=0.573)
4. No statistically significant differences were detected among the mean values of hemoglobin Fr (x 2x2=1,715; p=0,1677), erythrocytes Fr (x 2 = 0,872 p=0,4578), leucocytes Fr (x 2=1,0276; p=0,4751), hematocrit Fr (x 2=1,1028; p=0,3509) in the four time intervals in the group of patients suffering RA.

Discussion

We were able to determine the treatment efficacy of the Methotrexate. Through the statistical analysis, we were able to determine significant differences among mean values of CRP in all of the four-time intervals. The number of pts whose CRP values (over and below 6 mg/l) were negative, increased over time. Others, however, had elevated values of CRP.

There were no statistically significant differences among the mean values of RF in the four-time intervals. Some pts had very high values of RF.

Patients were administered over and below 30 JU/ml. Over time, the number of patients with negative RF values increased, however, there were no statistically significant differences. Patients that had high values of RF had a bigger progression of joint damage in certain periods of follow-up RA activity. Six months after the beginning of the Methotrexate therapy, there was visible clinical suppression of RA.

According to reports of several studies, we were able to determine the mutual correlation between variables of inflammation and reactants of the acute phase.

There are different approaches to RA treatment and a lot of clinical studies point out that it is difficult to assess which factors are significant predictors of a treatment outcome. [15-18].

Studies that deal with disease activity as a predictor for treatment outcome are inconsistent in their reports. The review of some studies shows that the inflammatory markers present at the beginning of RA when therapy had started, have no predictive significance in the overall treatment outcome.

On the other side, newer studies show that positive RF is a predictor of disease activity (RA) and radiographic progression (high values of RF are the predictor of consecutive joint damage). This was confirmed in our study as well. [19-22].

Other studies propose that RF levels are not predictors of a treatment outcome. A study shows that the positive RF of patients in the early stages of the disease that undergo intensive therapy proved to be prognostically significant for treatment outcomes. This occurs at the beginning of the study. This can be confirmed in our study as well.

RF is an indicator of the stage of the disease, some studies say. Other clinical variables measured in the first stages of the disease, however, vary in the influence on later joint damage.

These clinical variables evaluate the disease activity by counting the inflammatory joints and the reactants of the acute phase. The disease is chronically active when there are elevated values of CRP and ESR. CRP shows more sensitivity to inflammation instead than ESR. CRP shows no influence on gender, age, anaemia, or other serum proteins. The combination of CRP and ESR has no additive predictive value. [22-25].

CRP shows to be the best indicator for detecting damage because it is a direct and sensitive marker that gives fast answers to the changes in the inflammatory synovitis compared to ESR. ESR is an indirect marker of inflammation.

Conclusion

Disease progression resumes even after the therapy with Methotrexate. This especially happens in patients that have high values of ESR, CRP, and RF, all of which show to be predictors for aggressive development of the disease. Early and aggressive treatment is needed in the high-risk groups of patients whose course of the disease shows to be developmentally aggressive.

References

1. Kuper IH, Van Leeuwen MA, Van Riel PLCM, Sluiter WJ, Houtman NM, Cats HA, VanRijswijk MH. Influence of a ceiling effect on the assessment of radiographic progression in rheumatoid arthritis during the first 6 years of the disease. J Rheumatol 1999; 26:268-76.
2. Belghomari H, Saraux A, Allain J, Guedes C, Youinou P, Goff PL. Risk factors for radiographic articular destruction of hands and wrists in rheumatoid arthritis. J Rheumatol 1999; 26: 2534-8.
3. Molenaar ETH, Edmonds J, Boers M, van der Heijde DMFN, Lassere M. A practical exercise in reading RA radiographs by the Larsen and Sharp methods. J Rheumatol 1999; 26: 746-8.
4. Guillemin F, Billot L, Boini S, Gerard N, Odegaard S, Kvien TK. Reproducibility and sensitivity to change of 5 methods for scoring hand radiographic damage in patients with rheumatoid arthritis. J Rheumatol 2005; 32: 778-86.
5. Plant MJ, Williams AL, O' Sullivan MM, Lewis PA, Coles EC, Jessop JD. Relationship between time-integrated c-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. Arthritis Rheum 2000; 43(7): 1473-7.
6. Kirwan JR. The relationship between synovitis and erosions in rheumatoid arthritis. Br J Rheumatol 1997; 36: 225-228.
7. Strand V, Sharp JT Radiographic data from recent randomized controlled trials in rheumatoid arthritis. Arthritis Rheum 2003; 48: 21-34.
8. Visser H, le Cessie S, Vos K, Breedveld FC, Hazes J. How to diagnose rheumatoid arthritis early: a prediction model for persistent(erosive) arthritis. Arthritis rheum 2002; 46: 357-65.
9. Redlich K, Hayer S, Ricci R. Osteoclasts are essential for TNF-a-mediated joint destruction. J Clin Invest 2002; 110:1419-27.
10. James R. O'Dell. Therapeutic strategies for rheumatoid arthritis. N Engl J Med 2004; 350:2591-2602.
11. Hoekstra M,van Ede AE, Haagsma CJ. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Ann Rheum Dis 2003; 62: 423-6.
12. Jansen LMA, van der Horst - Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkmans BAC. Predictors of radiographic joint damage in patients with early rheumatoid arthritis. Ann Rheum Dis 2001; 60: 924-027.
13. Ten Klooster PM, Versteeg LGA, Oude Voshaar MAH, de la Torre I, De Leonardis F, Fakhouri W, et all Radiographic progression can still occur in individual patients with low or moderate disease activity in the current treat-to-target paradigm: real-world data from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Arthritis Res Ther. 2019;21(1): 237.
14. Darrah E, Yu F, Cappelli LC, Rosen A, O'Dell JR, Mikuls TR. Association of Baseline Peptidylarginine Deiminase 4 Autoantibodies With Favorable Response to Treatment Escalation in Rheumatoid Arthritis. Arthritis Rheumatol. 2019;71(5):696-702.
15. Fautrel B, Nab HW, Brault Y, Gallo G. Identifying patients with rheumatoid arthritis with moderate disease activity at risk of significant radiographic progression despite methotrexate treatment. RMD Open. 2015; 1(1): e000018.
16. Edwards CJ, Kiely P, Arthanari S, Kiri S, Mount J, Barry J, et all. Predicting disease progression and poor outcomes in patients with moderately active rheumatoid arthritis: a systematic review. Rheumatol Adv Pract. 2019; 3(1): rkz002.

17. Boeters DM, Nieuwenhuis WP, Verheul MK, Newsum EC, Reijnierse M, Toes RE, Trouw LA, van der Helm-van Mil AH.MRI-detected osteitis is not associated with the presence or level of ACPA alone, but with the combined presence of ACPA and RF..Arthritis Res Ther. 2016;18:179.
18. Lykke Midtboll. Structural damage and hand bone loss in patients with rheumatoid arthritis Dan Med J 2018;65(3): B5452.
19. Azzouzi H, Ichchou L.Bone Loss and Radiographic Damage Profile in Rheumatoid Arthritis Moroccan Patients. J Bone Metab. 2021;28(2):151-9.
20. Joo YB, Bang SY, Ryu JA, et al. Predictors of severe radiographic progression in patients with early rheumatoid arthritis: A Prospective observational cohort study. Int J Rheum Dis. 2017;20:1437–46.
21. Iwata T, Ito H, Furu M, et al. Periarticular osteoporosis of the forearm correlated with joint destruction and functional impairment in patients with rheumatoid arthritis. Osteoporos Int. 2016;27:691–701.
22. Mochizuki T, Yano K, Ikari K, et al. Correlation between hand bone mineral density and joint destruction in established rheumatoid arthritis. J Orthop. 2017;14:461–5.
23. Compston J. Glucocorticoid-induced osteoporosis: an update. Endocrine. 2018;61:7–16.
24. Heinze G, Wallisch C, Dunkler D. Variable selection - A review and recommendations for the practising statistician. Biom J. 2018;60:431–49.
25. Wehmeyer C, Pap T, Buckley CD, et al. The role of stromal cells in inflammatory bone loss. Clin Exp Immunol. 2017;189:1–11.